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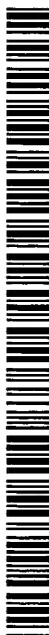
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**WO 03/022249 A1**

(54) Title: **NEW SELF EMULSIFYING DRUG DELIVERY SYSTEM**

(57) Abstract: The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising (i) one or more NO-releasing NSAID(s); (ii) one or more surfactants, of which at least one is phospholipid; said composition forming an *in-situ* oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise an additional oil or semi-solid fat. Further, one or more short-chain alcohols can optionally be included in the composition. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and said proton pump inhibitor is enteric coated.

## NEW SELF EMULSIFYING DRUG DELIVERY SYSTEM

5 Field of the invention

The present invention is directed to a new pharmaceutical composition in form of an emulsion pre-concentrate, a unit dosage form comprising said composition, its use in therapy as well as a process for the preparation thereof.

10

Background and prior art

Non-steroidal anti-inflammatory drugs, commonly abbreviated NSAIDs, are well-known drugs for the treatment of pain and inflammation. One of the major drawbacks with NSAIDs is that they have severe gastro-intestinal side effects. Patients undergoing treatment with NSAIDs for a longer period of time, such as naproxen, often experience problems with stomach gastrointestinal side effects.

20 Nitrogen oxide releasing NSAID compounds (in the following NO-releasing NSAIDs), have recently been found to have an improved side-effect profile, see e.g. WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

NO-releasing NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by Amidon et al. (*Pharm. Res.* 12 (1995) pp. 413-420). Drugs of this class are characterised by low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited, resulting in poor bioavailability upon oral administration.

30

WO 95/08983 discloses a self-emulsifying composition for oral administration that forms a microemulsion *in situ* when in contact with biological fluids. This composition can be characterised as a self-microemulsifying drug delivery system (SMEDDS), and comprises

- 5 at least
- an active compound,
  - a lipophilic phase consisting of a mixture of glycerides and fatty acid esters,
  - a surface-active agent,
  - a co-surfactant, and
  - 10 - a hydrophilic phase, which is achieved after ingestion by the physiological liquid of the digestive medium.

The present invention distinguishes in several aspects from WO 95/08983 and other SMEDDS.

- 15 US 5 929 030 discloses pre-concentrate of a microemulsion as a suitable pharmaceutical composition for a water-insoluble pharmaceutically active substance such as cyclosporin. The composition, that forms a microemulsion, comprises a) a water-insoluble pharmaceutically active material; b) a lipophilic phase comprising a mixture of glycerides, and c) a phospholipid and another surfactant.

- 20 Whereas the compositions disclosed in WO 95/08983 and in US 5 929 030 form a microemulsion *in situ*, the compositions of the present invention form an emulsion. EP 274 870 discloses a pharmaceutical composition comprising a non-steroidal anti-inflammatory drug (NSAID) and a surfactant, the composition being capable of forming micelles containing the NSAID upon oral administration. These micelles have been found
- 25 to present a particularly appropriate form to administer NSAIDs orally, alleviating their adverse effects on the gastrointestinal tract (GIT). Micelles are aggregates in which the surfactant molecules are generally arranged in a spheroidal structure with the hydrophobic region at the core shielded, in an aqueous solution, from the water by a mantle of outer hydrophilic regions. The drug is usually solubilised in the surfactant. Micelles are to be
- 30 contrasted in terms of their structure with emulsions, which are formed by compositions of the present invention. Whereas micelles are thermodynamically stable one-phase-systems (according to the Gibbs phase law) in which the aggregates usually have a diameter of

approximately two lengths of the surfactant molecule forming it, i.e. in the order of some ten to hundred Ångström (Å), emulsions are much larger aggregates, in the order of nanometers to micrometers in diameter, consisting of an oily core which is surrounded by one or several layers of surfactants. Emulsions are generally two-phase-systems, and they are thermodynamically unstable (but may be kinetically stable). Another major difference between the compositions of EP 274 870 and the present invention is the nature of the active compound. Whereas NSAIDs are crystalline powders by nature, the NO-releasing NSAIDs or mixtures of NO-releasing NSAIDs used in the present invention are in oil form or in a semisolid form. Moreover, micelles usually require a much higher drug:surfactant ratio compared to the oil:surfactant ratio required to form an emulsion.

One of the unique features with NO-releasing NSAIDs is that many of these compounds are oils or thermosoftening semisolids, which are practically insoluble in water. With high-dose NO-releasing NSAIDs, e.g. when the dose is above about 350 mg, it is difficult to formulate a tablet of reasonable size of the large amount of oil or semisolid. The lipophilic NO-releasing NSAIDs can, however, be formulated as oil-in-water emulsions where the compound constitutes, or is part of, the oil phase emulsified in water by one or more surfactants. An addition of a lipophilic solubiliser phase is not needed for the present invention since the active compound, the NO-releasing NSAID, is able to solely constitute the oil phase of the *in situ* emulsion. Further, the addition of a co-surfactant can be avoided by the present invention, i.e. the toxicological concern is reduced to a minimum.

In pharmacokinetic animal studies it has been surprisingly found that such oil-in-water emulsions of NO-releasing NSAIDs display a much better bioavailability compared to the unemulsified substance. A problem with emulsions is, however, that they are thermodynamically unstable and have poor long-term storage stability since they often tend to coalescence, creaming/sedimentation or phase separation. It is *inter alia* not possible to fill oil-in-water emulsions into gelatine capsules since the high water content of the emulsion is incompatible with the capsule shell and would dissolve it.

Outline of the invention

The problems mentioned above have now been solved by providing a novel Self  
5 Emulsifying Drug Delivery System, commonly known as SEDDS, suitable for oral  
administration. More particularly, the present invention is directed to a pharmaceutical  
composition suitable for oral administration, in form of an emulsion pre-concentrate,  
comprising

- 10 (i) one or more NO-releasing NSAID(s);  
(ii) a phospholipid optionally together with one or more other surfactants;  
(iii) optionally an oil or semi-solid fat;

said composition forming an *in-situ* oil-in-water emulsion upon contact with aqueous  
15 media such as gastrointestinal fluids.

The composition according to the present invention may optionally further comprise one or  
more short-chain alcohols.

20 The composition will form an *in situ* oil-in-water emulsion of small droplets of nanometer  
to micron size upon contact with gastrointestinal fluids, the droplets being constituted of  
one or more NO-releasing NSAIDs forming the core of the droplet, which is covered by  
one or several layers of surfactant. The *in situ* formed oil-in-water emulsion will provide a  
good bioavailability of the NO-releasing NSAID upon oral administration. Storage  
25 stability of the emulsion is not a concern since the emulsion is not formed until the pre-  
concentrate has been taken by the patient, i.e. first at the moment of administration. The  
possibly unpleasant taste of the pre-concentrate is not a problem when filled into capsules.

The pharmaceutical composition according to the present invention is an emulsion pre-concentrate at the time of administration to a patient. The emulsion pre-concentrate can be filled into unit dosage forms such as capsules, drinking ampoules and dose cushions, or may alternatively be formed as other suitable dosage forms such as chewable soft pills and chewy-base lozenges.

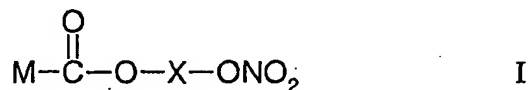
Upon contact with aqueous media such as gastrointestinal fluids, the emulsion pre-concentrate transforms into an oil-in-water emulsion. Thus, the composition will form an *in-situ* oil-in-water emulsion in the gastrointestinal tract (GI tract). The drug release rate of the composition is determined by the droplet size of the *in situ* emulsion and the polarity of the emulsion droplets, the latter being governed by the hydrophilic-lipophilic balance (HLB) of the drug/surfactant mixture, and the concentration of the surfactant. Generally, small droplet size and high polarity gives rise to a high drug release rate (*N.H. Shah et al., Int. J. Pharm.* 106 (1994), pp. 15-23).

The wording "NSAID" is defined as a non-steroidal anti-inflammatory drug, i.e. any drug having an anti-inflammatory effect, but which compound does not belong to the compound class "steroids". A person skilled in the art will know whether a compound falls under the definition NSAID. Examples of specific NSAIDs are naproxen, diclofenac, aceclofenac, indomethacine, ketorolac, sulindac, meloxicam, piroxicam, tenoxicam, ibuprofen, ketoprofen, naproxen, azapropazon, nabumetone, carprofen, tiaprofenic acid, suprofen, indoprofen, etodolac, fenoprofen, fenbufen, flurbiprofen, bermoprofen, pirazolac, zaltoprofen, nabumetone, bromfenac, ampiroxicam, and lornoxicam. This list should however not be considered as exhaustive in any way. The wording "NO-releasing NSAID" is contemplated to include any non-steroidal anti-inflammatory drug (NSAID), a salt or an enantiomer thereof, which has the capability to release nitrogen oxide.

NO-releasing NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by Amidon *et al. (Pharm. Res.* 12 (1995) 413-420). Drugs of this class are characterised by

low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited resulting in poor bioavailability upon oral administration.

- 5 Preferred NO-releasing NSAIDs in accordance with the present invention, are compounds of the formula I

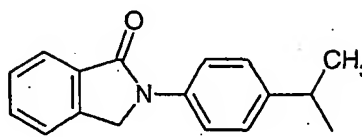
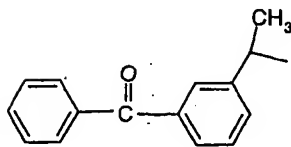
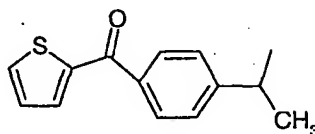
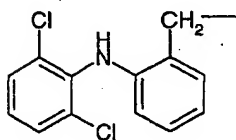


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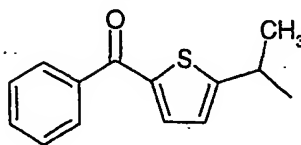
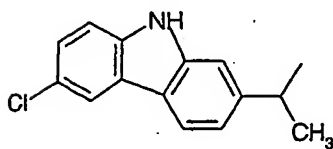
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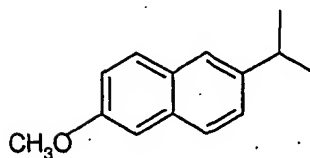
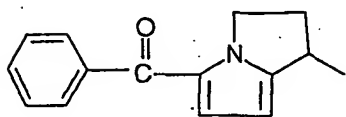
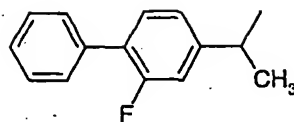
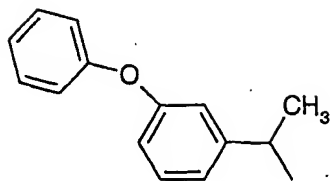
X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID; and

- 15 M is selected from anyone of

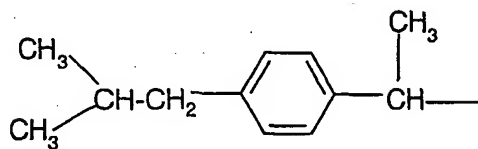
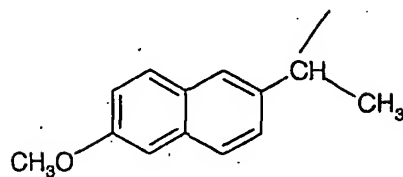
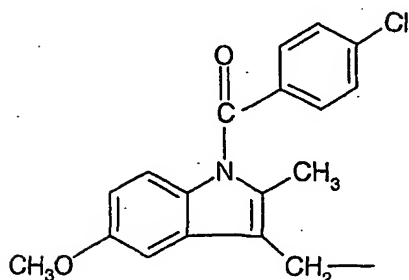


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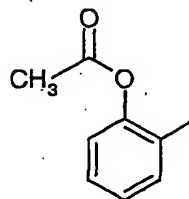




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and



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In a preferred embodiment of the invention, the spacer X is selected from a linear, branched or cyclic alkylene group  $-(CH_2)_n$  wherein n is an integer of from 2 to 10; and  $-(CH_2)_m-O-(CH_2)_p-$  wherein m and p are integers of from 2 to 10; and  $-(CH_2)_p-C_6H_4-CH_2-$  wherein p is an integer from 2 to 10.

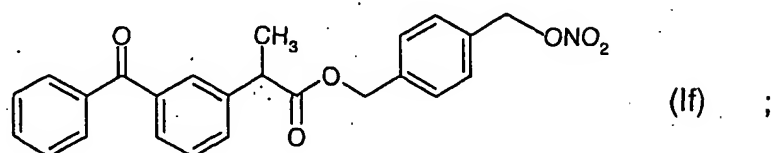
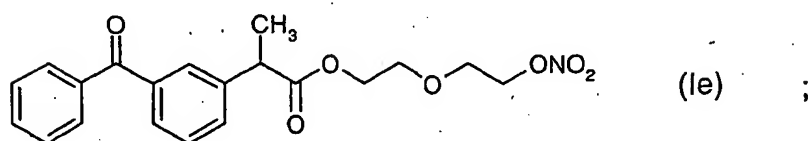
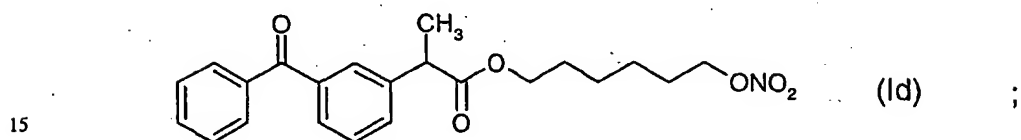
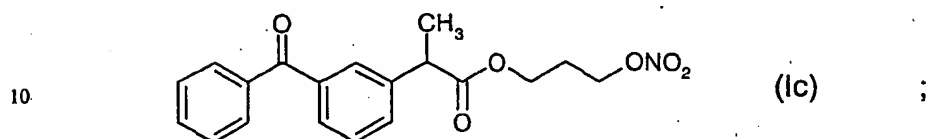
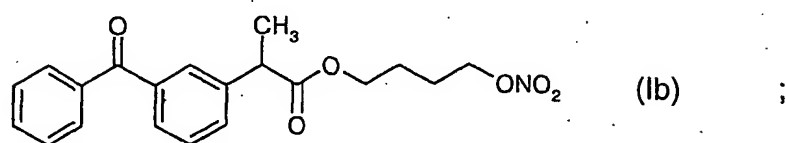
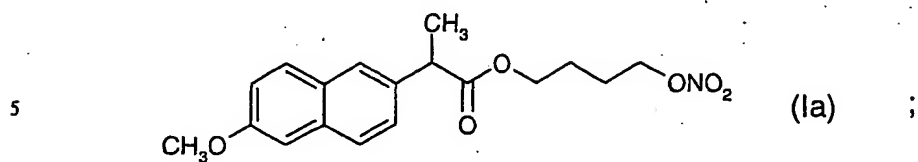
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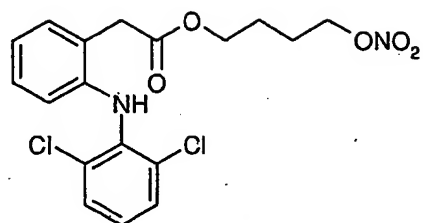
In one embodiment of the invention, NO-releasing NSAIDs contemplated as active compound(s) in the SEDDS formulation according to the present invention, are compounds disclosed and claimed in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641, which are hereby incorporated by reference.

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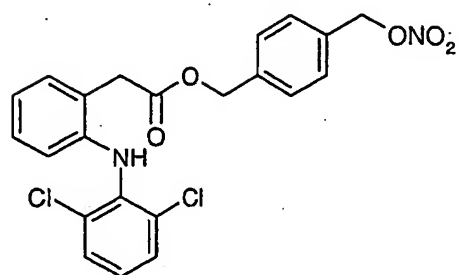


Specific NO-releasing substances useful in accordance with the present invention are

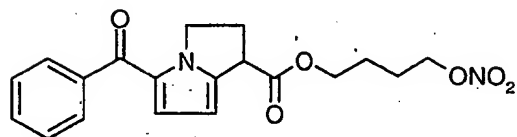




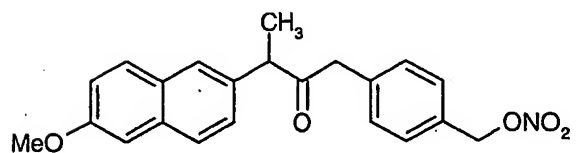
(Ig) ;



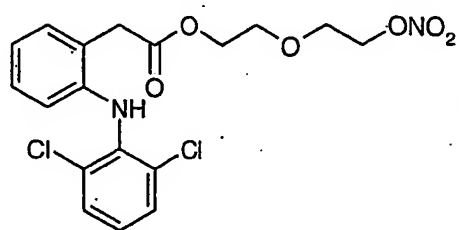
(Ii) ;



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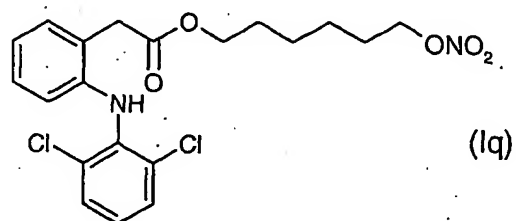
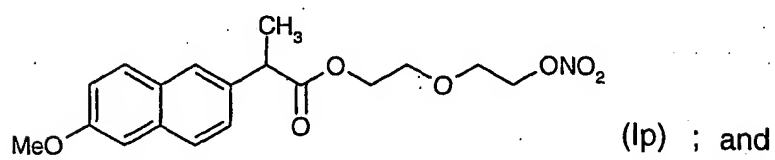
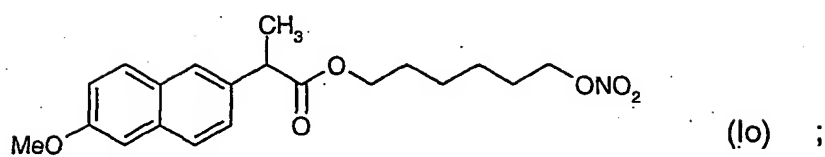
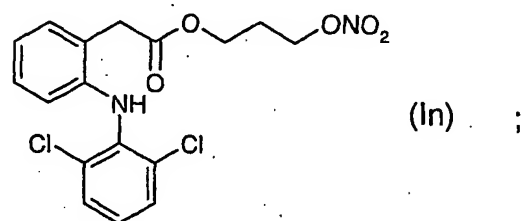
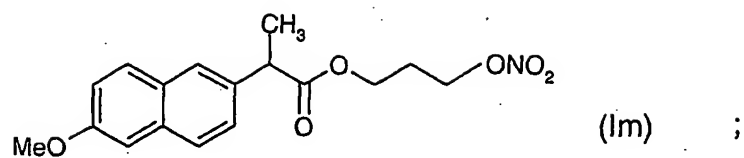


(Ik) ;



(IL) ;

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NSAIDs are by nature in form of a powder, whereas NO-releasing NSAIDs predominantly provide a compound in semisolid form or in oil form as such, due to the spacer. This unique feature provides the advantage that no external lipophilic oil or semisolid matrix needs to be added to the emulsion pre-concentrate, since this is an inherent feature of the drug. Additionally, a pharmacologically inert oil or semisolid fat may be added to the pharmaceutical composition by means of a filler or as a viscosity regulator. A filling agent may be required to increase dosing accuracy for low dose compounds. A viscosity regulator may be required in order to adjust optimal viscosity for filling of the composition into e.g. capsules. In particular high speed liquid filling of capsules requires careful adjustment of viscosity within a range that prevents splashing on the low viscosity end and thread-formation on the high viscosity end. Moreover, the viscosity range must be chosen so as to give a pumpable formulation. The viscosity range typically required for liquid filling of capsules is from 0.1 to 25 Pa s.

The total amount of NO-releasing NSAID(s) used in the composition of the invention is preferably in the range 50-1500 mg per unit dose. In still a further preferred embodiment, the amount of NO-releasing NSAID(s) used in the composition is 125-500 mg per unit dose.

The wording "unit dose" is defined as the amount of active compound administered in one single capsule, or dissolved in one glass of water.

The wording "phospholipid" is defined as a non-ionic surfactant comprising a phosphatidyl choline, a diglyceride linked to a choline ester of phosphoric acid. Different fatty acids are bound to the glyceride such as stearic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid. The origin of the phospholipid determines the content of the fatty acids linked.

Further, the phosphatidylcholine can be hydrogenated as well, i.e. the fatty acid moieties have been modified. The phospholipids used can be of both natural origin or synthetic.

Natural phospholipids are, for example, lecithin. Natural phospholipids are a mixture of various phospholipids and accompanying substances. The content of phosphatidylcholine

indicates the product, for example, LIPOID E80, denotes composition with egg lecithin comprising a specified mixture of the chains. Any lecithin can be used but the preferred lecithins are from soya or egg. Suitable lecithins are LIPOID<sup>®</sup> S40 (soya lecithin) and LIPOID<sup>®</sup> E80 (egg lecithin). The number defines the content of phosphatidylcholine.

5

The wording "surfactant" is defined as surface-active amphiphilic compounds such as block co-polymers. Preferred surfactants in accordance with the present invention are non-ionic surfactants, for example those containing polyethylene glycol (PEG) chains, particularly block co-polymers such as poloxamers.

10

Examples of suitable poloxamers are Poloxamer 407 (Pluronic F127<sup>®</sup>); Poloxamer 401 (Pluronic L121<sup>®</sup>); Poloxamer 237 (Pluronic F87<sup>®</sup>); Poloxamer 338 (Pluronic F138<sup>®</sup>); Poloxamer 331 (Pluronic L101<sup>®</sup>); Poloxamer 231 (Pluronic L81<sup>®</sup>); tetrafunctional polyoxyethylene polyoxypropylene block copolymer of ethylene diamine, known as Poloxamine 908 (Tetronic 908<sup>®</sup>); Poloxamine 1307 (Tetronic 1307<sup>®</sup>); Poloxamine 1107 polyoxyethylene polyoxybutylene block copolymer, known as Polyglycol BM45<sup>®</sup>. This list is only intended to serve as exemplification of surfactants that may be used in accordance with the present invention, and should not in any way be considered as exhaustive or as limiting the invention.

20

Also a co-surfactant may be added the surfactant above. The co-surfactant has a property as an enhancer of the emulsifying effect of the surfactant. Co-surfactant suitable for the unit dosage form of the invention is, for example, caprylocaproyl macroglycerides.

25

The total amount of surfactant(s) per unit dosage form in accordance with the invention may be within the range of from 12.5-6000 mg, preferably of from 100-500 mg. The amount phospholipid is 5-20% by weight, of the total amount of surfactants. The ratio NO-releasing NSAID:phospholipid/surfactant may vary from 1:0.1 to 1:10, preferably from 1:0.3 to 1:3.

30

All phospholipids, surfactants and co-surfactants described above are commercially available from e.g. LIPOID, BASF, Dow Chemicals, and Gattefossé.

In one aspect of the present invention, an oily (lipophilic) or semi-solid NO-releasing  
5 NSAID is used as the active ingredient.

If additional oil is added to the pharmaceutical composition this may be any oil as long as it is inert and compatible with the capsule material, as well as being acceptable for use in pharmaceuticals. A person skilled in the art will appreciate which oil to select for the  
10 intended purpose. Examples of suitable oils that may be used in accordance with the present invention are vegetable oils such as coconut oil, corn oil, soybean oil, rape seed oil, safflower oil and castor oil. Also animalic oils such as fish oil or one or more mono-, di- and triglycerides are suitable for the purposes of the present invention.

15 If a semi-solid fat is used as a filler for the pharmaceutical composition, this may preferably be selected from mono-, di- and triglycerides, and fatty acid alcohol such as stearyl alcohol, Gelucires 33/01<sup>®</sup>, 39/01<sup>®</sup>, 43/01<sup>®</sup>, glyceryl palmitostearate such as Precirol ATO5<sup>®</sup>. Gelucire<sup>®</sup> is a mixture obtained by mixing mono-, di-, and tri-esters of glycerol, mono- and di-esters of polyethylene glycol, or free polyethylene glycol.

20

If an additional oil or semi-solid fat is used in the pharmaceutical composition according to the invention, this may serve as a filler or as a viscosity regulator.

The wording "short-chain alcohols" used in accordance with the present invention is herein  
25 defined as linear or branched mono-, di- or tri-alcohols having 1-6 carbon atoms. Examples of such short-chain alcohols useful in accordance with the invention are ethanol, propylene glycol and glycerol.

If a short-chain alcohol is added to the pharmaceutical composition according to the  
30 invention, the solubility is enhanced and a smaller amount of surfactant is required.

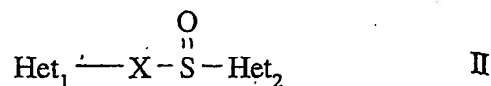
In another aspect of the invention, two or more NO-releasing NSAIDs are used as active ingredients, where anyone of said drugs may be present as an oil or as a semi-solid, or where at least one of said drugs is present as an oil or as a semi-solid and the other one(s) may be present as a solid which is dissolved or suspended in the oily or semi-solid compound. Combinations of two or more NO-releasing NSAIDs may be advantageous in case the high NO-load of a high-dose low potent NO-releasing NSAID is desired to be supplemented with a low dose of high potent NO-releasing NSAID.

10 A further aspect of the invention is a combination of one or more NO-releasing NSAIDs and an acid susceptible proton pump inhibitor (PPI) compound. The NO-releasing NSAIDs should be formulated such that it is emulsified in the stomach, i.e. as a SEDDS formulation as described above, while the acid susceptible proton pump inhibitor (PPI) must be protected from contact with the acidic gastric juice by for instance an enteric coating. The enteric coating layered PPI remain unaffected until it reaches the intestine, where the PPI is released. Individually prepared enteric coating layered units of the proton pump inhibitor (PPI) may be mixed into the SEDDS melt. Alternatively the PPI's may be filled into a capsule filled with solidified SEDDS, where a layer of protective paraffin may be needed between SEDDS and the prepared PPI pellets. In still an alternative embodiment the prepared PPI pellets may be mixed into a liquid SEDDS formulation.

The combination may thus either be a fix combination, i.e. as a formulation where the NO-releasing NSAID(s) and the acid susceptible proton pump inhibitor are mixed and thereafter filled into a suitable dosage unit. In an alternative embodiment of the invention the acid susceptible proton pump inhibitor may be filled into a capsule with an already solidified SEDDS formulation of one or more NO-releasing NSAID(s) – in this case a layer of protective paraffin or other inert material may be required between the SEDDS formulation and the acid susceptible proton pump inhibitor. In still an alternative embodiment the acid susceptible proton pump inhibitor is mixed into a liquid SEDDS formulation of the NO-releasing NSAID(s).

In an alternative embodiment of the invention, the NO-releasing NSAID(s) and the PPI may be provided in form of a kit, where the NO-releasing NSAID and the PPI are administered sequentially, i.e. one after the other. The order of administration is not crucial, meaning that either of the NO-releasing NSAID or the PPI may be administered before the other. Thus, one embodiment of the invention comprises a combination treatment where one or more NO-releasing NSAIDs are administered to a patient in need of treatment, whereafter a PPI is administered, or vice versa.

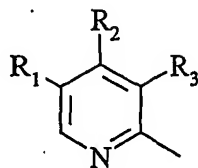
- 10 Examples of proton pump inhibitors suitable in a combination with a NO-releasing NSAID in accordance with the present invention as stated above, is a compound of the general formula II or a pharmaceutically acceptable alkaline salt thereof, or one of its single enantiomer or an alkaline salt of the single enantiomer:



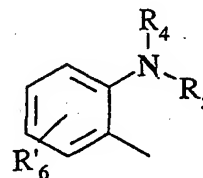
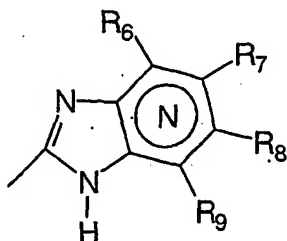
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wherein

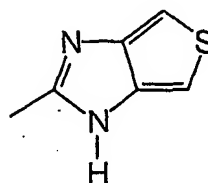
Het<sub>1</sub> is



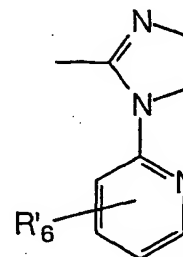
or

20 Het<sub>2</sub> is

or

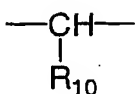


or

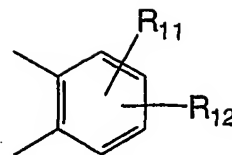


X =





or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub>

optionally may be exchanged for a nitrogen atom without any substituents;

R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen, alkyl and aralkyl;

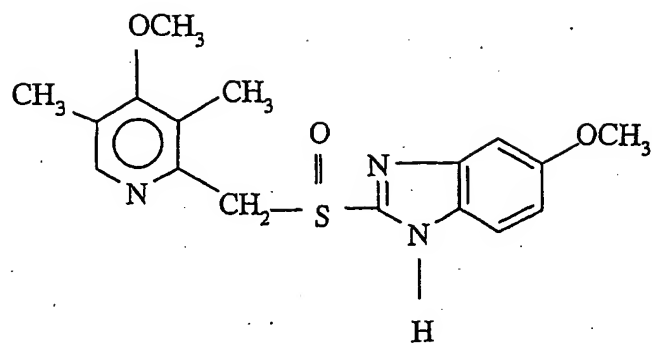
R<sub>6</sub>' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R<sub>6</sub>-R<sub>9</sub> are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R<sub>6</sub>-R<sub>9</sub> form ring structures which may be further substituted;

R<sub>10</sub> is hydrogen or forms an alkylene chain together with R<sub>3</sub> and

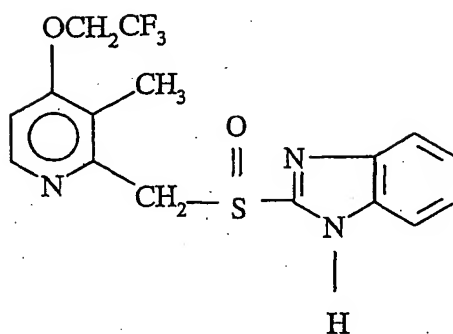
R<sub>11</sub> and R<sub>12</sub> are the same or different and selected from hydrogen, halogen or alkyl; alkyl groups, alkoxy groups and moieties thereof, they may be branched or straight C<sub>1</sub> - C<sub>9</sub>-chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

Examples of specific proton pump inhibitors suitable in accordance with the present invention are

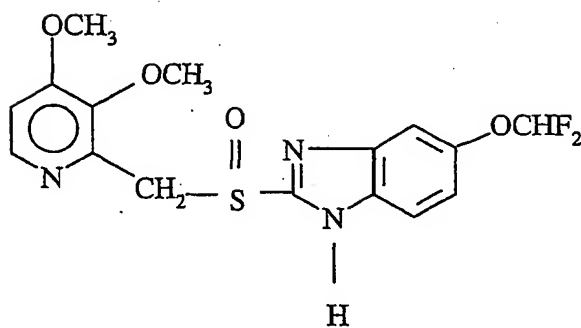


Omeprazole

5

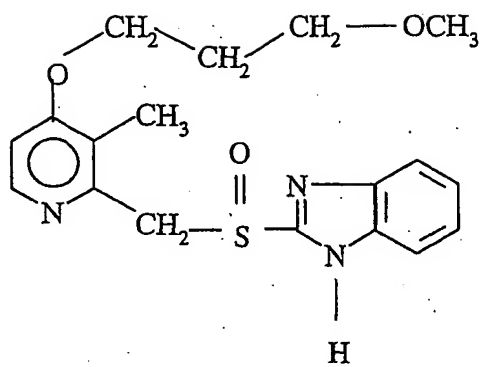


Lansoprazole

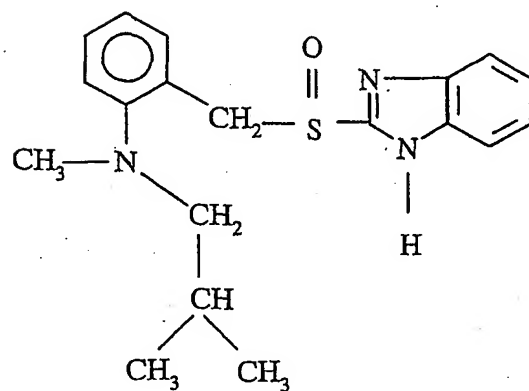


Pantoprazole

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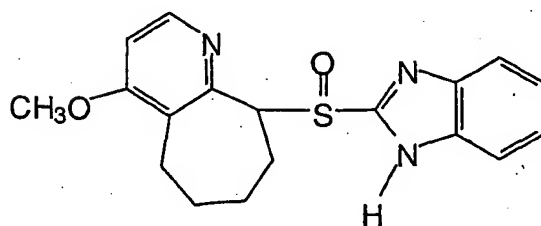
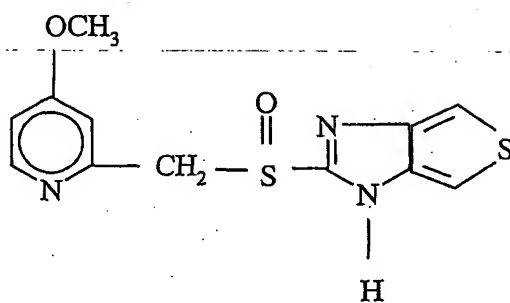


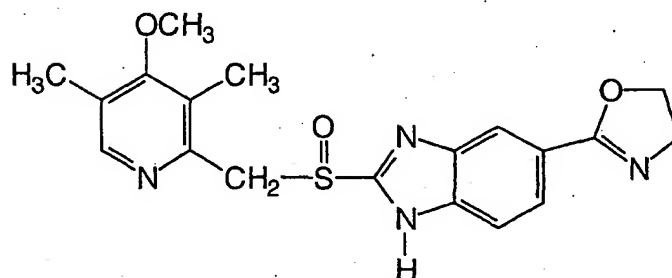
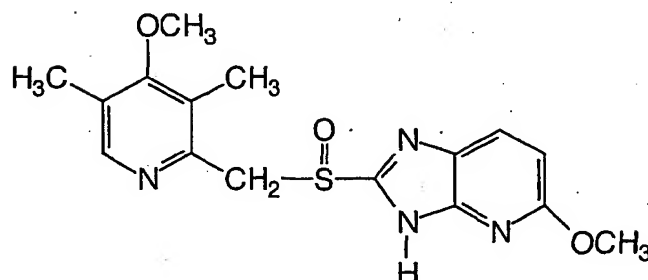
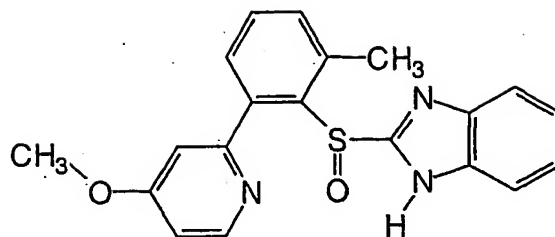
Pariprazole



Leminoprazole

5





5

The acid susceptible proton pump inhibitors used in the dosage forms of the invention may be used in their neutral form or in the form of an alkaline salt, such as for instance the  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Na^+$ ,  $K^+$  or  $Li^+$  salts, preferably the  $Mg^{2+}$  salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of the substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

10

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO 90/06925, and further especially suitable compounds are described in WO 95/01977 and WO94/27988.

15

The proton pump inhibitors used in a combination in accordance with the present invention, are preferably provided as enteric coating layered pellets comprising the acid

susceptible proton pump inhibitor. For the composition of the enteric coating layered pellets and its preparation, reference is made to WO 96/01623, which is hereby incorporated by reference.

5 Suitable combinations in accordance with the present invention are for instance a NO-releasing NSAID of the formula Ia and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole; or a NO-releasing NSAID of the formula Ii and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole.

10

The pharmaceutical composition of the invention is filled into unit dosage forms suitable for oral administration, such as capsules, drinking ampoules and dose cushions, or may be formulated as other suitable oral unit dosage forms such as chewable soft pills and chewy-base lozenges.

15

In a preferred embodiment of the invention, the pharmaceutical composition is filled into hard gelatine capsules, but capsules from alternative materials such as methyl cellulose-based shells, and soft gelatine capsules may also be used.

20

In an alternative embodiment of the invention, the pharmaceutical composition may be dissolved in e.g. a glass of water, thus allowing the pre-concentrate to form an emulsion which may be administered as such. The compositions intended for dissolution prior to administration may be filled e.g. into soft gelatine capsules, plastic or aluminium cushions, or plastic or glass ampoules. This feature is particularly advantageous for high dose  
25 compositions, which would require a large capsule, for patients who have difficulty in swallowing capsules, and for paediatric patients.

30

In a preferred embodiment the pharmaceutical composition of the present invention is filled into capsules. Preferred capsules are gelatine capsules, which may be soft or hard.  
The hard gelatine capsule consists of two pieces, a cap and a body, one fitting inside the

other. The hard gelatine capsules are produced empty and filled in a separate operation step. The soft gelatine capsule is a capsule, which is manufactured and filled, in one single operation.

5 As mentioned above, the emulsion pre-concentrate transforms into an oil-in-water emulsion upon contact with the gastrointestinal fluids, whereby the active drug is released. Thus, the composition will form an *in situ* oil-in-water emulsion in the gastrointestinal tract (GI tract).

10 The pharmaceutical composition of the present invention is particularly useful in the treatment of pain and inflammation. The wording "pain" is intended to include, but not limited to, nociceptive and neuropathic pain or combinations thereof; acute, intermittent and chronic pain; cancer pain; migraine and headaches of similar origin. The wording "inflammation" is intended to include, but not limited to, rheumatoid arthritis;  
15 osteoarthritis; and juvenile arthritis.

#### Methods of preparation

The pharmaceutical composition of the present invention may be prepared mainly by the following alternative methods:

20

##### ***I. Mixing***

a) The oily or semi-solid NO-releasing NSAID is put in a vessel, phospholipid, and optionally, a solid, semi-solid surfactant or solid/oily fat is added. The mixture is gently heated, making the formulation fluid, mixed thoroughly until homogenous (visual  
25 inspection) and the pre-concentrate is filled into capsules suitable for oral administration.  
b) Alternatively, the oily NO-releasing NSAID is put in a vessel and phospholipid, and optionally, a fluid surfactant is added. The mixture is mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral  
administration.

30

c) In a further alternative method, the oily NO-releasing NSAID is put in a vessel together with phospholipid, and finely grinded (particle size < 177  $\mu\text{m}$ ) solid surfactant is added. The liquid mixture is mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.

5

d) In still an alternative method the phospholipid and optionally, a semi-solid/solid surfactant (s) are put in a vessel, and one or more alcohols are added. The mixture is heated to the temperature corresponding to the melting point of the excipients, making the formulation fluid, mixed thoroughly until homogenous (visual inspection). The NO-releasing NSAID is added, and the mixture is mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration.

10

e) In yet a further alternative method the phospholipid optionally in mixture with a liquid surfactant(s) is put in a vessel, and one or more alcohols are added. The mixture is blended thoroughly until homogenous (visual inspection). The NO-releasing NSAID is added, and the mixture is mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration.

15

In order to fill a two-piece capsule or a soft gel capsule with a liquid, the formulation must be within a certain viscosity range, as determined by the manufacturer, at the filling temperature suitable for the process. For a two-piece capsule the maximum filling temperature is roughly 70 °C. The viscosity of the formulation should normally be in the range 50-1000 cPoise (=0.05-1 Pas) at the temperature chosen for the filling process. For the filling of the formulation into soft gel capsules, process temperature is not allowed to exceed 30-40 °C (the exact temperature depending on the manufacturer). The formulation must be liquid and have a viscosity that allows it to be pumpable at the filling temperature. In order to make the formulation liquid with an acceptable viscosity, several additives may be used, for example Cremophor EL<sup>®</sup> or fractionated coconut oil.

25

30

## II. Filling

For the filling procedure it is required that the composition is in liquid form at the temperature of filling. Semisolid thermosoftening compositions are therefore filled above the liquefying temperature. Soft gelatine capsules are manufactured and filled in one operation, and may be filled at temperatures of up to 40 °C, whereas hard gelatine capsules may be filled at temperatures of up to 70 °C. Hard gelatine capsules filled with compositions that remain liquid at storage temperature require sealing, e.g. by gelatine banding, to prevent leakage. The process of liquid filling of hard gelatine capsules and product requirements are e.g. described in *W.J. Bowtle, Pharmaceutical Technology Europe, October 1998*; *V.M. Young, Pharmaceutical Manufacturing and Packaging Sourcer, March 1999*; and *E.T. Coole, Pharmaceutical Technology International, September/October 1989*. Using two piece capsules permits filling of more than one phase into a single capsule, which may be desired for bi-or multiphase drug release (*W.J. Bowtle et al., Int. J. Pharm. 141 (1996), pp. 9-16*). Several phases of solidifying material can be filled in single steps. The final phase may be liquid if required. The number of phases is only restricted by the capsule size, and volume of the single phases. This special feature may also allow controlled release or separation of different drug substances formulated in the same capsule. Additionally, capsules may be processed further, e.g. by enteric coating.

## III. Combination with PPI's

The oily or semi-solid NO-releasing NSAID is put in a vessel, phospholipid and optionally a solid or semi-solid surfactant and optionally a solid/oily fat is added. The mixture is gently heated, making the formulation fluid, mixed thoroughly until homogenous (visual inspection) and prepared enteric coating layered pellets comprising an acid susceptible proton pump inhibitor are added to the mixture. The pre-concentrate with the suspended PPI-pellets is filled into capsules, where it solidifies, suitable for oral administration.

Alternatively the oily or semi-solid NO-releasing NSAID is put in a vessel, solid surfactant and solid/oily fat (optional) is added. The mixture is heated to the temperature corresponding to the melting point of the excipients, making the formulation fluid, mixed



thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration, where it solidifies. A protective layer of paraffin, or any other inert thermo softening base suitable for oral administration, is added and allowed to solidify. On top of the paraffin, the prepared PPI-pellets are added.

5

In still an alternative method, the oily NO-releasing NSAID is put in a vessel, phospholipid and optionally a fluid surfactant are added. The mixture is mixed thoroughly until homogenous (visual inspection), and the prepared PPI-pellets are added to the mixture. The pre-concentrate with suspended PPI-pellets is filled into capsules suitable for oral administration.

10

#### *IV. Characterisation of the formulations*

In order to characterise formulations, the time required for the formulation to form an oil-in-water emulsion upon contact with simulated gastric fluid, SGF, (without enzymes), is determined, and the formed emulsion is characterised. SGF comprises of 7 millilitres concentrated hydrochloric acid, 2 grams of sodium chloride and distilled water to give the solution a total volume of 1 L. The "emulsion-forming test" is performed in test tubes (beaker) with magnetic stirring. The test tube, containing a small magnet, is filled with 12.5 ml SGF without enzymes, corresponding to one tenth of the average volume of gastric fluid in humans, and formulation corresponding to one tenth of the dose of active compound is added. If the formulation being characterised is a combination with a PPI, the PPI-pellets are checked in order that they are unaffected by the SGF, which is made by visual inspection. If the enteric coating of the PPI-pellets is affected, the PPI may be affected negatively in pH=1.2, and this can be observed as a marked change in colour.

25

The time for emulsion formation will vary from 30 seconds and up to 15 minutes, depending on the composition of the formulation. If one or more short-chain alcohols are added, the time for emulsion formation will vary between 2-3 seconds and 3-4 minutes.

30

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

5

In the following examples, the active compound used in the formulation was a compound of the formula (Ia) above.

Formulation were prepared by dissolving the phospholipid in a co-solvent such as  
10 propylene glycol, glycerol or ethanol, and then adding the active compound to the mixture:

***Formulation 1***

Lipoid S100	0.30 g
Propylene glycol	0.90 g
15 Compound of formula Ia	4.00 g

***Formulation 2***

Lipoid S100	0.30 g
20 Glycerol	0.90 g
Compound of formula Ia	4.00 g

***Formulation 3***

25 Lipoid S100	0.24 g
Etanol	0.96 g
Compound of formula Ia	4.00 g

**Formulation 4**

Lipoid E80	0.30 g
Propylene glycol	0.90 g
Compound of formula Ia	4.00 g

5

**Formulation 5**

Lipoid E80	0.30 g
Glycerol	0.90 g
Compound of formula Ia	4.00 g

10

**Formulation 6**

Lipoid E80	0.30 g
Ethanol	0.90 g
Compound of formula Ia	4.00 g

15

**Formulation 7**

Lipoid S75	0.30 g
Propylene glycol	0.90 g
Compound of formula Ia	4.00 g

20

**Formulation 8**

Lipoid S75	0.30 g
Glycerol	0.90 g
Compound of formula Ia	4.00 g

25

**Formulation 9**

Lipoid S75	0.30 g
Ethanol	0.90 g
Compound of formula Ia	4.00 g

30

The emulsifying formulations were tested in a self-emulsifying test (described on page 24)

The dissolution of the drug was measured according to the paddle method in US Pharmacopoeia (US Pharmacopoeia 24/NF 19, 200).

5

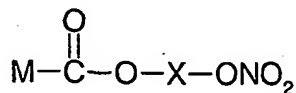
Formulation	Time to emulsion formation	Amount (%) dissolved drug after 200 minutes
1	1-2 minutes	6-8
2	1-2 minutes	6-7
3	1-2 minutes	8-10
4	1-2 minutes	8-10
5	1-2 minutes	8-10
6	1-2 minutes	8-10
7	1-2 minutes	10-13
8	1-2 minutes	8-10
9	1-2 minutes	10-13

The bioavailability of the formulations according to the present invention may be tested by oral administration in fastened minipigs.

10

Claims

1. A pharmaceutical composition suitable for oral administration, in form of an emulsion  
5 pre-concentrate, comprising
- (i) one or more NO-releasing NSAID(s);
- (ii) a phospholipid;
- 10 said composition forming an *in-situ* oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids.
2. A pharmaceutical composition according to claim 1, comprising
- 15 (i) one or more NO-releasing NSAID(s);
- (ii) a phospholipid
- (iii) one or more surfactants.
3. A pharmaceutical composition according to any one of claims 1-2, further comprising  
20 an oil or a semi-solid fat.
4. A pharmaceutical composition according to any one of claims 1-3, further comprising one or more short-chain alcohols.
- 25
5. A pharmaceutical composition according to any one of claims 1-4, wherein the NO-releasing NSAID is a compound of the formula I



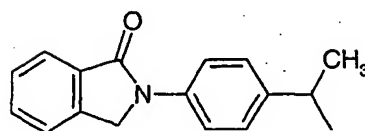
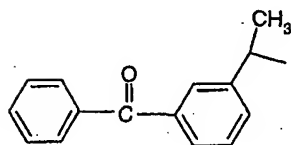
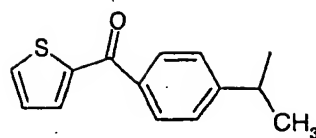
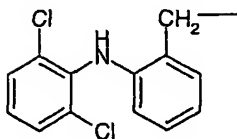
I

wherein

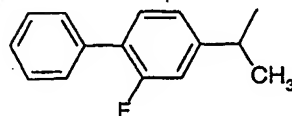
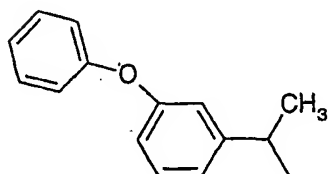
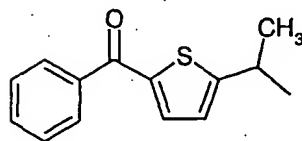
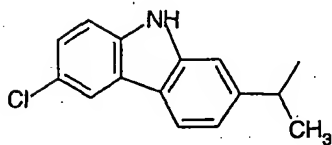
X is a spacer; and

M is selected from anyone of

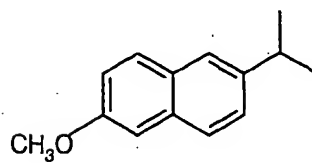
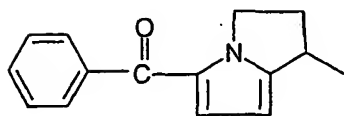
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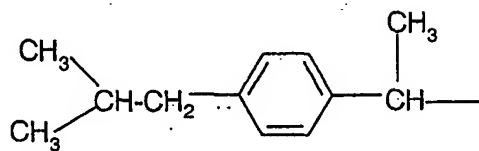
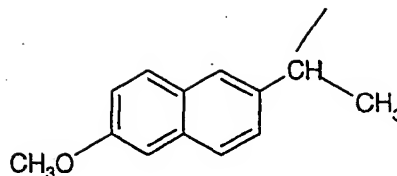
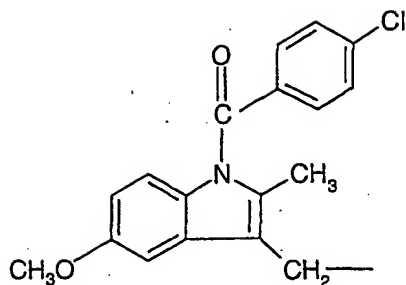


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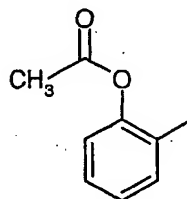


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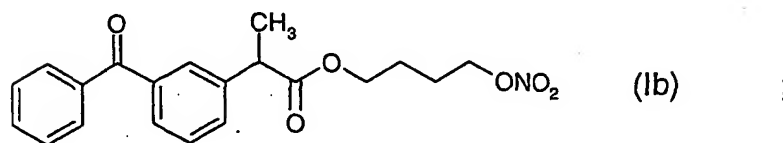
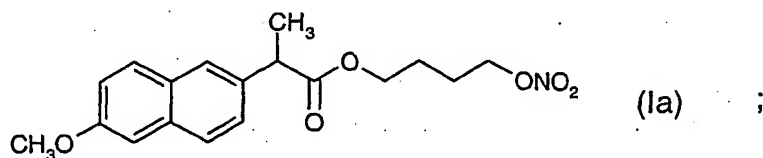
6. A pharmaceutical composition according to claim 5, wherein the spacer X of the NO-releasing NSAID is selected from a linear, branched or cyclic alkylene group:

$(\text{CH}_2)_n$  wherein n is an integer of from 2 to 10;  $-(\text{CH}_2)_m\text{-O-}(\text{CH}_2)_p-$  wherein m and p are integers of from 2 to 10; and  $-(\text{CH}_2)_p\text{-C}_6\text{H}_4\text{-CH}_2-$  wherein p is an integer of from 2 to 10.

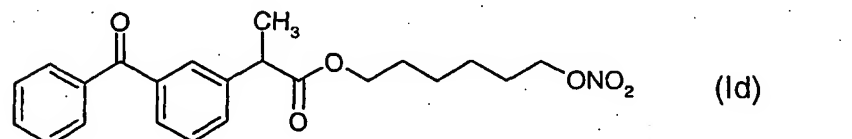
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7. A pharmaceutical composition according to any one of claims 1-6, wherein the NO-releasing NSAID is any one compound selected from

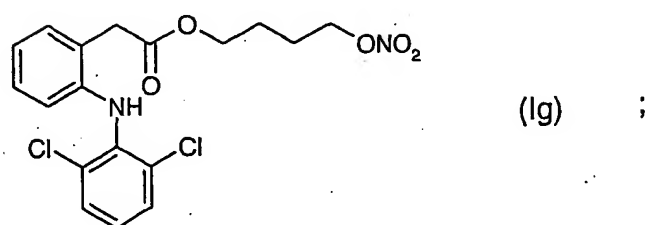
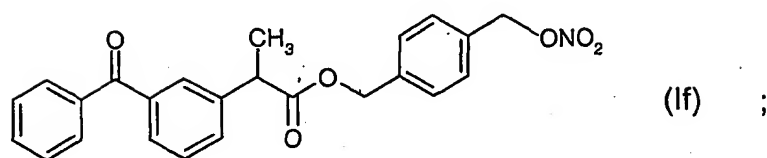
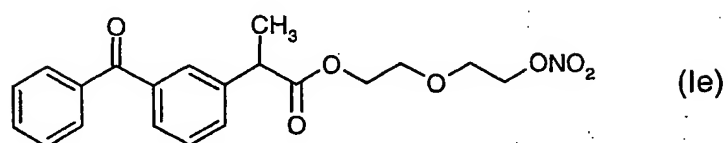
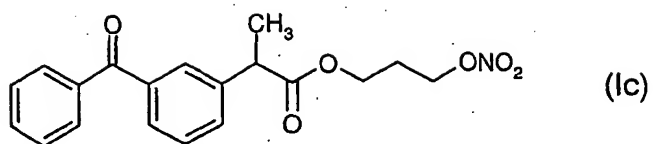
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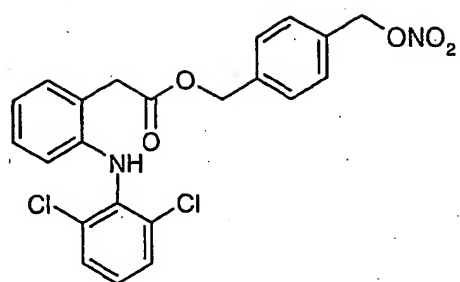
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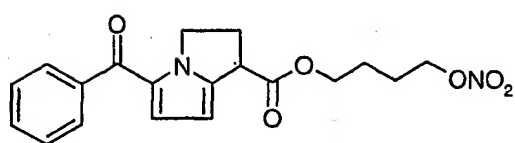
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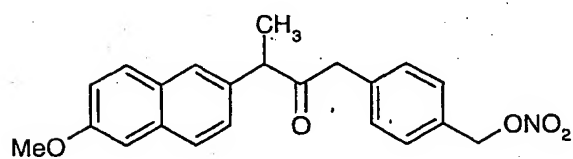




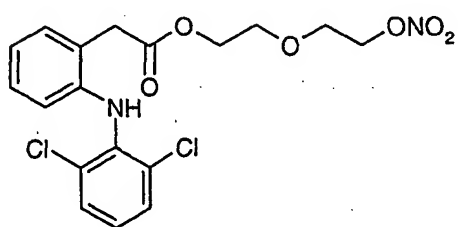
(li) ;



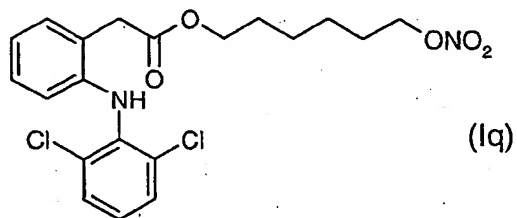
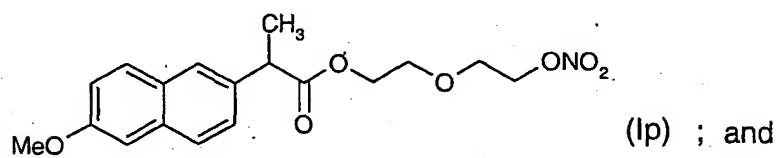
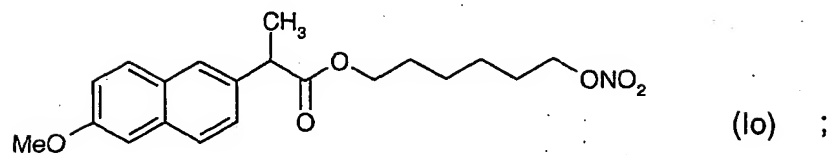
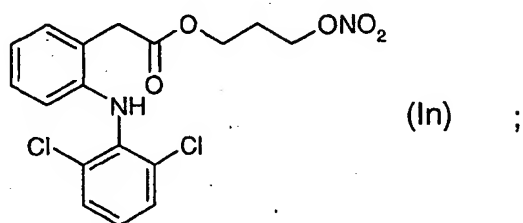
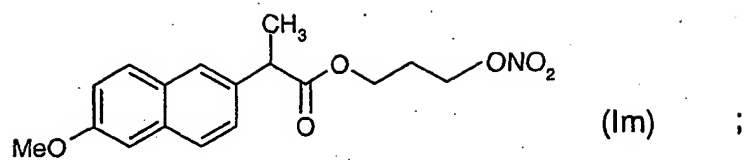
(lj) ;



(lk) ;

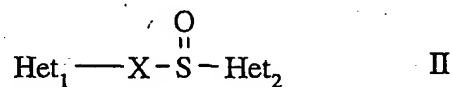


(IL) ;



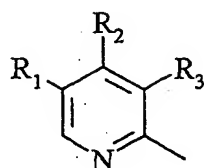
8. A pharmaceutical composition according to any one of claims 1-7, further comprising individually enteric coating layered units of an acid susceptible proton pump inhibitor, or a pharmaceutically acceptable alkaline salt thereof.

9. A pharmaceutical composition according to claim 8, wherein the acid susceptible proton pump inhibitor is selected from a compound of the general formula II or a pharmaceutically acceptable alkaline salt thereof, or one of its single enantiomer or an alkaline salt of the single enantiomer

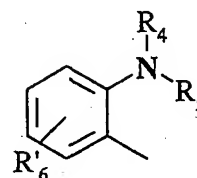


wherein

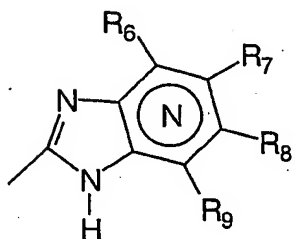
10 Het<sub>1</sub> is



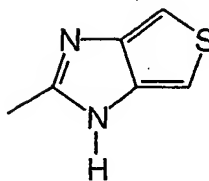
or



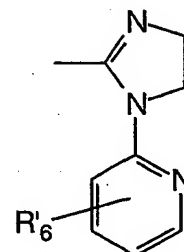
Het<sub>2</sub> is



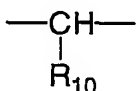
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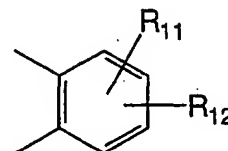
or



15 X =



or



wherein

- N in the benzimidazole moiety means that one of the carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any substituents;

R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

5 R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen, alkyl and aralkyl;

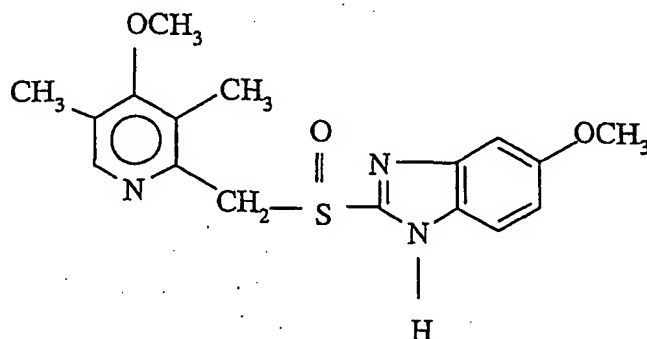
R<sub>6</sub>' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

10 R<sub>6</sub>-R<sub>9</sub> are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R<sub>6</sub>-R<sub>9</sub> form ring structures which may be further substituted;

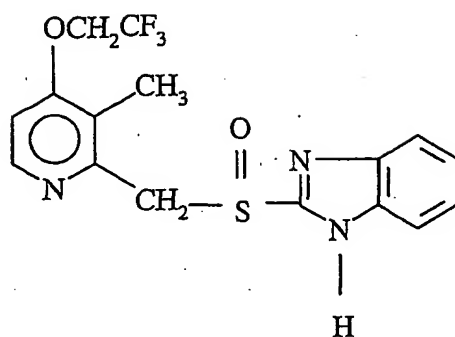
R<sub>10</sub> is hydrogen or forms an alkylene chain together with R<sub>3</sub> and

15 R<sub>11</sub> and R<sub>12</sub> are the same or different and selected from hydrogen, halogen or alkyl; alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C<sub>1</sub> - C<sub>9</sub>-chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

20 10. A pharmaceutical composition according to claim 9, wherein the acid susceptible proton pump inhibitor is selected from the group consisting of

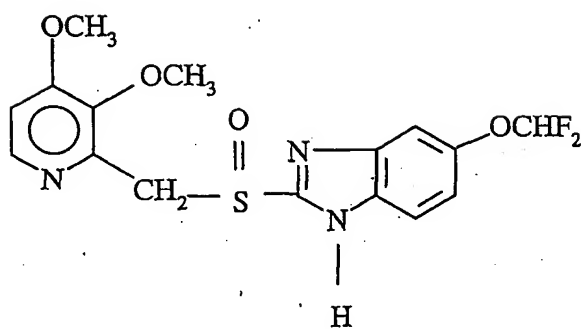


Omeprazole

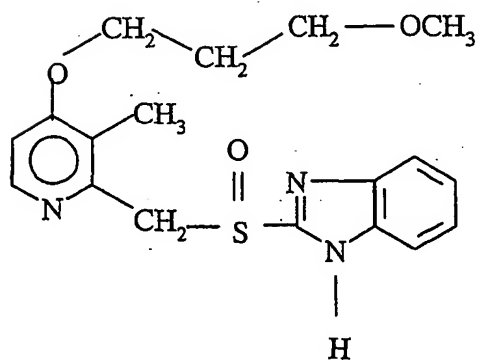


Lansoprazole

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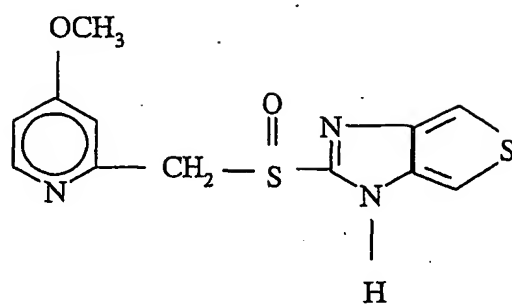
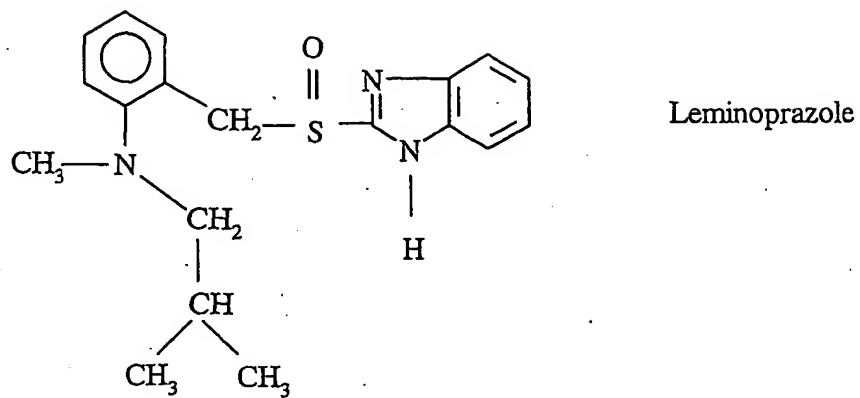


Pantoprazole

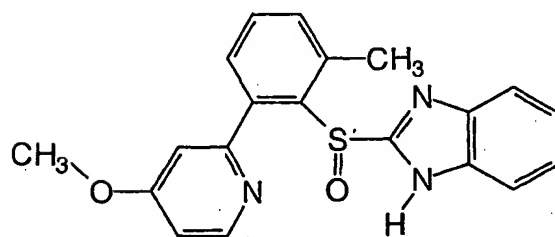
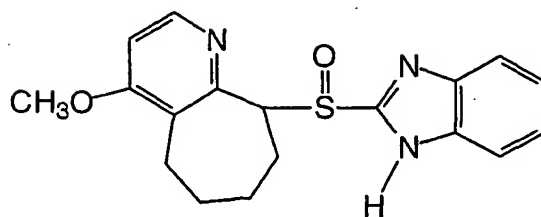


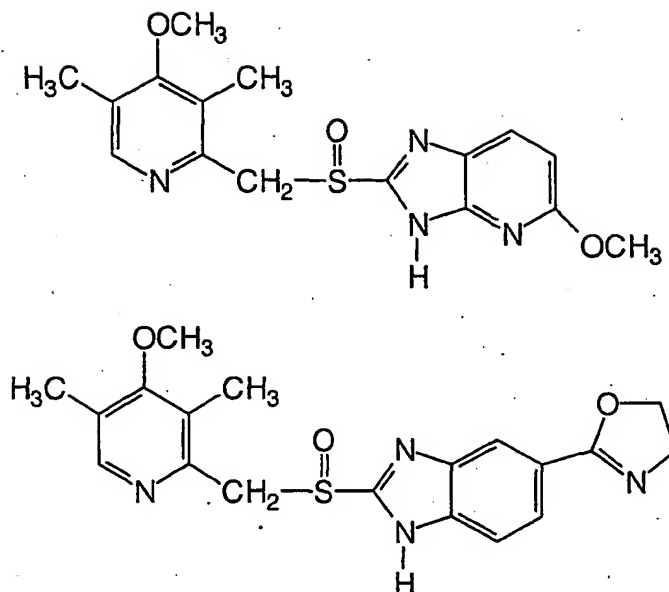
Pariprazole

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11. A pharmaceutical composition according to claim 10, wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt of omeprazole,  
 5 (S)-omeprazole and an alkaline salt of (S)-omeprazole.

12. A pharmaceutical composition according to claim 11, wherein the alkaline salt of omeprazole or (S)-omeprazole is a magnesium salt.

10 13. A pharmaceutical composition according to claim 8, wherein the NO-releasing NSAID is a compound of formula Ia and the acid susceptible proton pump inhibitor is selected from the group consisting of omeprazole, an alkaline salt of omeprazole, (S)-omeprazole and an alkaline salt of (S)-omeprazole.

15 14. A pharmaceutical composition according to any one of claims 1-13, wherein the amount of the NO-releasing NSAID is from 50-1500 mg per unit dose.

15. A pharmaceutical composition according to claim 14, wherein the amount of the NO-releasing NSAID is from 125-500 mg per unit dose.

16. A pharmaceutical composition according to any of claims 1-15, wherein the phospholipid is lecithin.

17. A pharmaceutical composition according to claim 16, wherein the lecithin comes from egg and soya, or a mixture thereof.

18. A pharmaceutical composition according to any one of claims 1-17, wherein the surfactant is a non-ionic surfactant.

19. A pharmaceutical composition according to any one of claims 1-18, wherein the non-ionic surfactant is a block co-polymer.

20. A pharmaceutical composition according to claim 19, wherein the non-ionic surfactant is a poloxamer.

21. A pharmaceutical composition according to claim 20, wherein the surfactant is selected from any one of Poloxamer 407; Poloxamer 401; Poloxamer 237; Poloxamer 338; Poloxamer 331; Poloxamer 231; Poloxamine 908; Poloxamine 1307; Poloxamine 1107; and polyoxyethylene polyoxybutylene block copolymer.

22. A pharmaceutical composition according to any one of claims 1-21, wherein the total amount of phospholipid together with surfactant(s) is from 12.5-6000 mg per dosage form.

23. A pharmaceutical composition according to claim 22, wherein the total amount of phospholipid and surfactant(s) is from 100-500 mg per dosage form.

24. A pharmaceutical composition according to any one of claims 1-23, wherein the ratio NO-releasing NSAID: phospholipid and the optional surfactant is within the range of from 1:0.1 – 1:10.



25. A pharmaceutical composition according to claim 24 wherein the ratio  
NO-releasing NSAID: phospholipid and the optional surfactant is within the range of from  
1:0.3 –1:3.
- 5 26. A pharmaceutical composition according to claim 3, wherein the oil is a vegetable oil.
27. A pharmaceutical composition according to claim 26, wherein the vegetable oil is  
selected from coconut oil, corn oil, soybean oil, rape seed oil, safflower oil and castor oil.
- 10 28. A pharmaceutical composition according to claim 26, wherein the oil is an animalic  
oil.
29. A pharmaceutical composition according to claim 28, wherein the animalic oil is a fish  
oil or one or more mono-, di- or triglycerides.
- 15 30. A pharmaceutical composition according to claim 3, wherein the semisolid fat is  
selected from mono-, di- and triglycerides.
31. A pharmaceutical composition according to claim 30, wherein the mono-, di- and  
20 triglycerides are selected from the group consisting of glyceryl palmitostearate, a mixture  
of mono-, di- and tri-esters of glycerol, mono- and di-esters of polyethylene glycol and free  
polyethylene glycol.
32. A pharmaceutical composition according to any one of claims 4-31, wherein the  
25 short-chain alcohol is selected from ethanol, propyleneglycol or glycerol.
33. A pharmaceutical composition according to any one of claims 1-32, further  
comprising a co-surfactant.

34. A unit dosage form filled with a pharmaceutical composition according to any one of claims 1-33.

35. A unit dosage form according to claim 34, selected from any one of capsules, drinking ampoules, dose cushion, chewable soft pill, and chewy-base lozenges.

36. A unit dosage form according to claim 35, in form of a capsule.

37. A unit dosage form according to claim 36, wherein said capsule is a hard gelatine capsule.

38. A unit dosage form according to claim 36, wherein said capsule is a soft gelatine capsule.

39. An oral solution comprising a pharmaceutical composition according to any one of claims 1-33 dissolved in water.

40. A kit comprising a pharmaceutical composition according to any one of claims 1-33 in a unit dosage form, in combination with an acid susceptible proton pump inhibitor.

41. A kit according to claim 40, wherein the proton pump inhibitor is enteric coated.

42. A kit according to claim 41, wherein the proton pump inhibitor is enteric coated omeprazol.

43. A method for the treatment of pain, whereby a pharmaceutical composition according to any one of the preceding claims, is administered to a patient in need of such treatment.

44. A method for the treatment of inflammation, whereby a pharmaceutical composition according to any one of the preceding claims, is administered to a patient in need of such treatment.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01598

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/107, A61K 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0166088 A1 (ASTRAZENECA AB), 13 Sept 2001 (13.09.01) --	1-44
X	US 5929030 A (Y. K. HAMIED ET AL), 27 July 1999 (27.07.99) --	1-44
X	WO 0057885 A1 (PHARMACIA & UPJOHN COMPANY), 5 October 2000 (05.10.00) --	1-44
A	WO 0072838 A1 (ASTRAZENECA AB), 7 December 2000 (07.12.00) --	1-44

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

4 December 2002

06-12-2002

Name and mailing address of the ISA/

Swedish Patent Office

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01598

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5932243 A (GERD FRICKER ET AL), 3 August 1999 (03.08.99)  --	1-44
A	EP 0984012 A2 (PFIZER PRODUCTS INC.), 8 March 2000 (08.03.00)  -- -----	1-44

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE02/01598**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **43-44**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet\***
2. ☒ Claims Nos.: **1**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**see next sheet\*\***
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

\*

Claims 43-44 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)).

Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions..

\*\*

The expression "NO-releasing NSAID(s)" covers a large number of compounds with different properties and industrial applicability for all of the claimed invention has not been demonstrated. Hence the search has been restricted to compositions comprising the compounds defined in claim 5.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/02

International application No.

PCT/SE 02/01598

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0166088	A1	13/09/01	AU	3787601 A	17/09/01
				AU	4634700 A	10/11/00
				EP	1186053 A	13/03/02
				SE	0000773 D	00/00/00
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				EP	0760237 A	05/03/97
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				BG	106158 A	28/06/02
				BR	0011116 A	19/02/02
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				TR	200103474 T	00/00/00
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				AT	172297 A	15/10/01
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				BE	1008329 A	02/04/96
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				JP	11315022 A	16/11/99
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				GB	9320463 D	00/00/00
				GB	9722958 D	00/00/00
				HK	1022258 A	00/00/00



### Information on patent family members

International application No.

PCT/SE 02/01598

Form PCT/ISA/210 (patent family annex) (July 1998)